Therapeutic Apheresis for Renal Disorders

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ABSTRACT

This review summarizes the clinical evidence and practical details for the use of plasmapheresis and other apheresis modalities for each indication in nephrology. Updated information on the molecular biology and immunology of each renal disease is discussed in relation to the rationale for apheresis therapy and its place among other available treatments. Autoantibody-mediated diseases, such as anti-GBM (anti-glomerular basement membrane) glomerulonephritis (GN), ANCA (antineutrophil cytoplasmic antibody)-related GN and the antibody-mediated type of TTP (thrombotic thrombocytopenic purpura), and alloantibody-mediated diseases such as kidney transplant sensitization and humoral rejection, can be treated by various plasmapheresis methods. These include standard plasmapheresis with a replacement volume, plasma exchange with online plasma purification using adsorption columns or secondary filtration. However, it should be noted that the pathogenic molecules implicated in FSGS (focal segmental glomerulosclerosis), myeloma cast nephropathy, and perhaps other diseases are too small to be removed by most online purification methods. A great majority of controlled trials and series on which evidence-based treatment recommendations are made were performed using centrifugal plasmapheresis; it is presumed that membrane-separation plasmapheresis is equally efficacious. For some rarer diseases, such as MPGN (membranoproliferative GN) type 2 with factor H abnormalities or C3Nef (C3 nephritic factor) autoantibodies, there are only a few case reports, but enough scientific understanding to warrant a trial of plasmapheresis in severe cases. Photopheresis, which is effective for cell-mediated rejections in heart and lung transplantation, has not yet found a place in the routine treatment of kidney transplant rejection.

Therapeutic plasmapheresis, sometimes known as plasma exchange (PLEX) or therapeutic plasma exchange (TPE), is used for many renal disorders. Other apheresis modalities, such as LDL-apheresis for nephrotic hypercholesterolemia or photopheresis for cell-mediated transplant rejection, are used rarely in nephrology practice.

TPE is used to treat many types of glomerulonephritis (GN) and renal vasculitis, thrombotic microangiopathies, paraproteinemias affecting the kidney, and kidney transplant alloantibodies. In many cases, there will be concurrent treatment with corticosteroids, immunosuppressive or cytotoxic medications. Plasmapheresis may be a first-line element in the treatment strategy, or reserved for a subset of cases, depending on the severity of disease. In many diseases, the molecule targeted for removal by TPE is an autoantibody. In others, the target may be an alloantibody, an antigen-antibody complex, a cryoglobulin, an immunoglobulin light chain, a nonimmunoglobulin protein, or sometimes, a still ill-defined pathogenic moiety. Advances in molecular science have identified the culprit molecule in an increasing number of renal diseases (Table 1).

There have been few controlled trials in the use of TPE in renal disease, and most of these trials have included patients with a variety of renal diseases. The limitations of these trials have been noted. In most cases, TPE is used as an adjunct to other treatment modalities. It is difficult to compare results from different trials, as the indications for and efficacy of TPE in each condition are determined by clinical experience and trial design (Table 2). The American Society for Apheresis (ASFA) Committee on Apheresis Applications has published the most complete review of relevant literature and recommendations (1). Most of the evidence has come from trials of TPE using centrifugal machines (1). TPE using membrane filtration is presumed to be of similar efficacy in most situations. A standard TPE procedure should remove, at each session, a volume of plasma that is 1.5 times the estimated circulating plasma volume of the patient. Thus, the volume of each procedure reflects only patient parameters, not disease characteristics.

In contrast, it is the type and severity of the disease being treated that dictate the frequency and total number of TPE treatments (i.e., the intensity and duration of therapy). Removal of the offending pathogenic material from the bloodstream is most convincingly attained by discarding the collected plasma and replacing it with an albumin solution or some combination of albumin, saline, and transfused plasma (2). In this review, these generalizations apply except where specific variances are mentioned. For instance, although albumin/saline
Membranous GN (primary idiopathic)

Kidney transplant rejection, antibody-mediated ("humoral") type

TABLE 1. Some prototypic renal diseases and the pathogenic molecules that are targets for removal by plasmapheresis therapy

<table>
<thead>
<tr>
<th>Renal disease</th>
<th>Pathogenic molecule in the plasma</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-glomerular basement membrane (anti-GBM) glomerulonephritis (GN) (including Goodpasture’s syndrome)</td>
<td>Autoantibody reactive with normally hidden faces of the EA and EB epitopes on noncollagenous (NC1) domains of α5 and α5 chains of collagen type IV</td>
<td>9,10</td>
</tr>
<tr>
<td>Alport’s posttransplantation glomerulonephritis</td>
<td>Alloantibody reactive with a normally exposed face of the EA epitope on intact noncollagenous (NC1) domain of α5 chain of collagen type IV</td>
<td>9,10</td>
</tr>
<tr>
<td>Antineutrophil cytoplasmic antibody (ANCA)-associated GN (&quot;pauci-immune&quot; focal necrotizing GN, and GN of microscopic polyangiitis and Wegener’s granulomatosis), and ANCA renal vasculitis</td>
<td>Autoantibodies active with myeloperoxidase, protease 3, other neutrophil lysosomal antigens, and possibly lysosomal-associated membrane protein-2</td>
<td>12,26,167</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis (FSGS), type that recurs posttransplantation</td>
<td>Circulating glomerular permeability factor(s) of 30–50 kDa. Recently implicated is a soluble form of the podocyte urokinase receptor (suPAR)</td>
<td>48,57</td>
</tr>
<tr>
<td>Myeloma cast nephropathy</td>
<td>Free kappa or lambda light chain</td>
<td>72</td>
</tr>
<tr>
<td>Hepatitis C-related membranoproliferative GN type 1 (MPGN 1) (and “cryoglobulinemic GN”), and hepatitis C renal vasculitis</td>
<td>Mixed cryoglobulins, type II or type III (cold-insoluble circulating immune complexes comprising viral antigen, IgG antibody, IgM rheumatoid factor, and complement proteins)</td>
<td>93,95</td>
</tr>
<tr>
<td>MPGN 2 (&quot;dense deposit disease&quot;), C3 nephritic factor (C3Nef) type</td>
<td>Autoantibody (called C3Nef) reactive with the C3 convertase (C3bBb complex) of the alternative pathway complement cascade</td>
<td>107–109</td>
</tr>
<tr>
<td>MPGN 2 (&quot;dense deposit disease&quot;), factor H deficiency type</td>
<td>(No noxious substance is removed by TPE, but replacement with transfused plasma replenishes Factor H, a regulatory protein of the alternative pathway complement cascade)</td>
<td>107,110</td>
</tr>
<tr>
<td>Renal thrombotic microangiopathy in TTP (thrombotic thrombocytopenic purpura), sporadic-type</td>
<td>Autoantibody reactive with the ADAMTS13 enzyme (von Willebrand factor cleaving enzyme). (Replace with transfused plasma, to replenish the depleted ADAMTS13 enzyme)</td>
<td>115,168</td>
</tr>
<tr>
<td>Catastrophic antiphospholipid syndrome</td>
<td>Anticardiolipin and antibeta-2-glycoprotein autoantibodies</td>
<td>131</td>
</tr>
<tr>
<td>Kidney transplant rejection, antibody-mediated (&quot;humoral&quot;) type</td>
<td>Alloantibody reactive with HLA antigen(s)</td>
<td>149</td>
</tr>
</tbody>
</table>

TABLE 2. Autoantibody-induced forms of glomerulonephritis do not benefit equally from TPE

<table>
<thead>
<tr>
<th>Glomerular disease</th>
<th>Pathogenic autoantibody reacts with</th>
<th>Evidence-based use of TPE and immunosuppressive medications</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>Anti-glomerular basement membrane (anti-GBM) glomerulonephritis (GN) (including Goodpasture’s syndrome)</td>
<td>α-Chain noncollagenous (NC1) domains of type IV collagen (see Table 1)</td>
<td>TPE only if serum creatinine &lt; 6 mg/dl, or to treat diffuse alveolar hemorrhage. Use cyclophosphamide and corticosteroids as well as TPE. If creatinine above 500 μmol/l (5.7 mg/dl) or on dialysis, usually too late to salvage renal function.</td>
<td>16</td>
</tr>
<tr>
<td>Antineutrophil cytoplasmic antibody ANCA-associated GN (&quot;pauci-immune&quot; GN)</td>
<td>Neutrophil lysosomal proteins: myeloperoxidase, protease 3, etc. (see Table 1)</td>
<td>TPE only if serum creatinine &gt; 6 mg/dl. If creatinine below 500 μmol/l (5.7 mg/dl) usually corticosteroid and cytotoxic drugs will suffice (without TPE). TPE is almost never indicated. Corticosteroids and cytotoxic drugs are used in selected cases; many patients get no specific treatment.</td>
<td>34,35,37</td>
</tr>
<tr>
<td>Membranous GN (primary idiopathic)</td>
<td>M-type phospholipase A2 receptor on podocyte foot processes (in 70% of adults) (see Ref. 169)</td>
<td>TPE is almost never indicated. Corticosteroids and cytotoxic drugs are used in selected cases; many patients get no specific treatment.</td>
<td>170,171</td>
</tr>
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</table>

This table exemplifies that the etiology of a disease may provide a rationale for a treatment strategy, but does not predict its response to treatment. These three types of glomerulonephritis (GN) are all autoantibody-induced, but show a range of different clinical indications for plasmapheresis therapy (TPE), corticosteroids, and other immunosuppressive drugs. Clinical indications are based on empirical evidence from clinical trials.

replacement suffices for most nephrological indications, fresh frozen plasma (FFP) replacement is required in thrombotic thrombocytopenic purpura (TTP), other thrombotic microangiopathies, catastrophic antiphospholipid syndrome (CAPS), pulmonary–renal syndrome with active lung hemorrhage, and membranoproliferative GN (MPGN) type 2 with factor H deficiencies (see below).

The use of devices that purify the plasma online is favored by some to avoid the need for replacement colloids, but the limitations of these systems must not be overlooked (2). For instance, “double filtration” plasmapheresis removes only proteins whose size exceeds about 100 kDa, so is unsuitable for treatment of focal segmental glomerulosclerosis (FSGS), light-chain glomerulopathy, and myeloma cast nephropathy.
Immunoadsorption columns that bind IgG are appropriate when the target molecule is known to be an IgG, preferably with monitoring of specific antibody levels.

**Anti-Glomerular Basement Membrane Disease**

Anti-glomerular basement membrane (anti-GBM) disease is an autoimmune disorder defined by the production of anti-GBM antibodies that result in a rapidly progressive GN (RPGN). Frequently, the antibodies also react with alveolar basement membrane, causing diffuse alveolar hemorrhage (DAH) (3). The term Goodpasture’s syndrome implies both kidney and lung involvement; the term Goodpasture’s disease denotes also that anti-GBM antibodies are present (4). Anti-GBM disease has a bimodal age distribution, with peak incidence in the third and sixth decades, and a slight male predominance (5). Approximately 30–40% of patients will have renal involvement only (5).

Almost all patients will have detectable anti-GBM antibodies in their blood, usually IgG (mainly IgG1), although IgM and IgA antibodies have been reported (6). These antibodies are directed against the noncollagenous domain 1 (NC1) of alpha chains of type IV collagen, which is a component of the alveolar and renal basement membranes (7,8). Originally, only antibody to the NC1 domain of z3 chains (anti-z3NC1) was detected, but now it is clear that anti-z5NC1 is also usually present. Both are reactive with sites that are normally folded below the surface of the z3z4z5 NC1 hexamer, so a conformational change in the NC1 domain has to occur (see Table 1) (9). This suggests one of two possibilities: either the first event in the pathogenesis is a disruption of the target molecule, causing a neo-antigen to be displayed that elicits the antibody response; or exposure to a different pathogenic stimulus induces the autoantibodies, which subsequently uncover the epitope (10).

Anti-GBM disease is rare, but comprises approximately 20% of patients presenting with a pulmonary-renal syndrome (6,8). The characteristic kidney pathology includes crescent formation in >50% of glomeruli and linear deposits of IgG and C3 on immunofluorescence microscopy (IFM) (5,11). Anti-GBM disease is almost always severe, with only 16% of cases in one large biopsy series having less than 50% crescents (12). It is important to distinguish anti-GBM disease from other causes of RPGN or pulmonary-renal syndrome, because anti-GBM disease requires earlier initiation of intensive TPE if there is to be an impact on outcome and mortality (see Table 2).

For over 30 years, the gold standard for treatment of anti-GBM disease has included a combination of TPE, cyclophosphamide, and corticosteroids (13,14). A single randomized controlled trial (RCT) and other nonrandomized case controlled studies have shown that TPE provides a more rapid decline in anti-GBM antibodies, improves renal recovery, decreases likelihood of end-stage renal disease (ESRD), reduces mortality, and achieves a more rapid resolution of hemoptysis in cases with DAH (14–18). Prior to the use of TPE in anti-GBM disease, nearly 90% of patients would either die or require long-term hemodialysis (19).

It is critical that TPE be applied early in the course of anti-GBM disease. Several studies have reported that those patients who present with a serum creatinine (Cr) < 500 μmol/l (5.7 mg/dl) will recover renal function, with a 5-year renal survival rate of 94% with intensive treatment (7,16). Patients who present with a Cr > 5.7 mg/dl or are dialysis-dependent at the time of initiation of TPE generally do not recover renal function (3,16). In this situation, TPE should only be performed if DAH is also present. DAH can be rapidly fatal, but responds to TPE in 90% of patients, so a low threshold should be present to initiate TPE (6).

The typical TPE regimen for anti-GBM consists of daily or every other day TPE for a minimum of 14 days, or until the anti-GBM antibody levels are undetectable (1,6,7,16). Replacement fluid is usually albumin; however, in the setting of DAH, FFP (1–2 l) should also be given during the last portion of the exchange (7). ASFA classifies anti-GBM disease as a category 1 indication for TPE (1). Staphylococcal protein A immunoadsorption (PAI) has been used in a small series of patients with anti-GBM disease (20,21). However, protein A immunoadsorption columns are no longer available.

In general, anti-GBM disease does not relapse and does not require long-term immunosuppression, although recurrence after remission has been reported (16,22). However, up to one-third of anti-GBM cases also have antineutrophil cytoplasmic antibody (ANCA) (6,8). These “double-antibody” patients behave clinically more like an ANCA-associated RPGN, and will probably require more long-term immunosuppression (5). In general, kidney transplantation is feasible, although it is recommended that anti-GBM antibodies be undetectable for at least 6 months to minimize the risk of recurrence (7,23).

Alport’s posttransplantation GN is an anti-GBM disease that occurs de novo in approximately 3–5% of renal transplant patients with Alport’s syndrome (6). As such patients congenitally lack an antigen on the NC1 domain of the z5 chain of type IV collagen, transplantation with a normal kidney that contains this antigen may elicit an antibody response. However, the antibody that is produced recognizes a surface epitope that is not identical to the one seen by the Goodpasture’s anti-z5NC1 antibody (see Table 1) (9). TPE is recommended for Alport’s posttransplant anti-GBM disease (and antitubular basement membrane disease) (24).

**Pauci-Immune RPGN and ANCA-Associated Disease**

Approximately 40% of patients with RPGN present with crescentic GN characterized by few or absent immune deposits on IFM, hence the term pauci-immune GN (11). Often, the disease is limited to the kidneys, usually a focal necrotizing GN, with or without demonstrable renal vasculitis. Many cases also have evidence of systemic small-vessel vasculitis, either microscopic polyangiitis (MPA) or Wegener’s granulomatosis...
(WG) (newly renamed granulomatosis with polyangiitis [GPA], and very rarely, Churg–Strauss syndrome, and are strongly associated with ANCA (25,26).

Some pauci-immune GN is of lesser severity, with up to 57% of cases having <50% crescents on biopsy (12). However, considering only RPGN cases with >50% crescents, ANCA-associated disease is still five times more common than anti-GBM disease (12). ANCA-associated disease can present with a range of systemic involvement, including lung, sinus, and neurologic symptoms (25). The presentation of the pulmonary–renal syndrome associated with ANCA is clinically similar to anti-GBM disease.

Untreated, generalized WG and MPA follow a progressive course to fatal organ failure, with a mean survival of 5 months (25). Untreated pauci-immune RPGN will progress to ESRD in 80% of cases (11). Since the 1970s, high-dose corticosteroids and cyclophosphamide have achieved remissions in 80–90% of cases; however, relapse is common (25,27). Those who present with advanced renal failure have poorer outcomes, with only 50% with independent renal function at 1 year (without TPE) (27). Three prospective controlled trials found no benefit of the addition of TPE to standard immunosuppressive therapy versus standard therapy alone; however, later subset analysis suggested that those with elevated Cr and dialysis dependency may benefit from TPE (28–30). A retrospective Japanese national survey that included 53 myeloperoxidase (MPO)-ANCA patients failed to demonstrate benefit from standard TPE or double filtration plasmapheresis (31).

However, several other RCTs have shown benefit in renal function with the addition of TPE to standard immunosuppression in a subset of patients with more advanced renal disease. Both TPE and immunoadsorption were shown to equally improve renal function in a prospective randomized trial including 38 patients with ANCA-associated rapidly progressive crescentic GN, with 70% off dialysis at the end of the study (32). Additionally, in another RCT, 10 of the 11 patients in the TPE group who presented with a Cr > 5.7 mg/dl recovered renal function, whereas only 3 of 8 similarly affected patients in the non-TPE group recovered to the same degree (33).

The European Vasculitis Study Group (EUVAS) has published four different RCTs that included patients with renal involvement: CYCAZAREM, MEPEX, CYCLOPS, and SOLUTION. However, only the MEPEX (Methyprednisone versus Plasma Exchange) study evaluated the benefit of TPE (34). In MEPEX, patients with severe renal involvement (Cr > 5.7 mg/dl or intention to initiate dialysis within 48 hours) were shown to derive the most benefit from addition of TPE to standard immunosuppressive therapy (27,35,36). At 3 months, renal recovery occurred in 49% in the methyprednisone group and in 69% of those who received TPE (p = 0.02). At 12 months, the addition of TPE was associated with a 24% reduction in risk for progression to ESRD (27). A multicenter international RCT is in progress to establish the efficacy of TPE in addition to immunosuppressive therapy and glucocorticoids at reducing death and ESRD in ANCA positive vasculitis.

In summary, TPE should be considered in conjunction with immunosuppression in the subset of patients with pauci-immune RPGN who present with severe renal disease (Cr > 5.7 mg/dl), dialysis dependence or when dialysis is imminent, and in cases with DAH. ASFA classifies RPGN without anti-GBM is a category II indication for TPE (1). Typical treatment regimen for TPE includes a 1–1.5 plasma volume exchange, with 5% albumin for replacement, with 1–21 of FFP if pulmonary hemorrhage is present (1,37). Consider daily TPE in fulminant cases or in presence of DAH, then every 2–3 days for a total of six to nine procedures (1).

**Idiopathic Immune-Complex RPGN**

Cases of RPGN in which IFM reveals a granular pattern of immunoglobulin deposition are classified as “immune-complex-mediated” or Couser Type II (38). Some are due to systemic lupus nephritis, IgA nephropathy or Henoch–Schonlein nephritis, but others are idiopathic. TPE treatment for idiopathic cases is reported in series that admix several etiologies including ANCA-related GN. For instance, in a randomized trial of standard immunosuppressive therapy with or without TPE in 39 cases of RPGN, only 6 had idiopathic type II RPGN (30). Overall TPE does seem to benefit severe cases of immune-complex RPGN, and is recommended by ASFA in the category “weak recommendation, moderate quality evidence” (1).

**Lupus Nephritis**

Systemic lupus erythematosus nephritis, particularly class IV diffuse proliferative disease, is often regarded as a prototypic immune-complex nephritis, but the large randomized prospective trial published in 1992 showed no benefit from the addition of TPE to a standard steroid and cyclophosphamide regimen (39). Subsequent trials in class IV lupus nephritis confirmed the same conclusion (40). Nevertheless, cases presenting as RPGN or with lung hemorrhage probably should receive TPE treatment (41).

**IgA Nephropathy and Henoch–Schonlein Nephritis**

IgA nephropathy is the most common cause of GN worldwide, but <50% of patients have a progressive deterioration in GFR over 20 years (11). A small percentage of cases present as RPGN, with crescentic changes on biopsy, and have been treated with TPE (42). Henoch–Schonlein purpura (HSP) is also IgA-mediated, mainly affecting children, and causes an immune-complex vasculitis of the skin, joints, GI tract, and a proliferative GN (43). Renal involvement from HSP is more frequent in adults, who may present with a crescentic RPGN picture.
Children and adults often receive treatment with steroids, cyclophosphamide, and other immunosuppressives, and in severe cases, TPE can be added, for instance, three times a week for 2 weeks and then weekly thereafter (43). No randomized trials have been reported, and published series using TPE have included more cases of HSP than IgA nephropathy. Although the literature may be colored by a positive publication bias, there are several series and cases where outcomes appear to improve with TPE use (44–47). Using TPE as the sole treatment to avoid drug side effects in children has also shown benefits compared with historical controls (42,44). For IgA RPGN, ASFA offers a “weak recommendation” for 1 to 2 weeks of TPE, as for other immune-complex RPGNs (1).

**Focal Segmental Glomerulosclerosis**

FSGS is a histologically defined group of glomerular diseases. The subset treatable by TPE recurs in kidney transplants, and appears to be due to circulating glomerular permeability factor(s) (48). This type of FSGS is distinct from those caused by genetic abnormalities of podocyte foot-process proteins (49), or secondary cases, such as those due to morbid obesity, vesicoureteral reflux, and HIV nephropathy (50). The increased prevalence of FSGS in patients of west-African ancestry is attributable to ApoL1 gene variants that arose because they confer resistance to trypanosomiasis, but at the cost of increased susceptibility to hypertensive and sclerotic glomerular damage (51).

The characterization of circulating permeability factors has remained elusive (52). Evidence for a 30- to 50-kDa glycoprotein has accumulated, although its chemical identity could not be established (53). Its proteinuric effect has been shown in vitro to be inhibited by binding to galactose (54). When incubated with isolated rat glomeruli, it causes massive albumin leakage (55). This is the basis of the “GVV assay,” which measures glomerular permeability factor activity in clinical serum samples (56).

Recently, a soluble form of the urokinase receptor found on podocytes (suPAR) has been implicated (57). Serum suPAR levels (22–45 kDa fragments) are elevated in 70% of patients with FSGS, but not in other glomerular diseases. In animal models, suPAR causes glomerular injury by activation of β3 integrin on podocyte foot processes. Activated β3 integrin was found on podocytes in kidney biopsies from FSGS cases, but not other glomerulopathies. Initial studies of TPE for recurrent FSGS show that clinical remission correlates with reduction in serum suPAR levels below about 2000 pg/ml. Moreover, at this level, the serum lost its ability to induce podocyte β3 integrin activity. Two patients in whom the TPE regimen failed to reduce suPAR levels below 2000 pg/ml did not achieve clinical remission, and their serum still strongly activated podocyte β3 integrin (57). Although still unconfirmed, and not applicable to all cases, this work holds great promise to further elucidate the etiology, and to impact treatment by TPE and other therapies.

The recurrence of FSGS after kidney transplantation has been known for four decades (58), and successful treatment by TPE is well established (59,60,61,62,63,64). FSGS recurs posttransplant in about 23% of adults (59). Rates are higher in children, or when a previous transplant has been lost to recurrence. TPE together with corticosteroids and cyclophosphamide is standard treatment, and mycophenolate and rituximab may be helpful (63). The diagnosis should be established by transplant biopsy as soon as heavy proteinuria appears, and treatment should begin immediately.

A recommended initial regimen is TPE daily for 3 days, then at least three times per week for the next 2 weeks (1). Thereafter, TPE two or three times per week can be continued until remission occurs, as judged by serial quantitation of urine protein and serum Cr. Some cases require prolonged maintenance TPE, perhaps weekly, to sustain remission. One series employed 17 TPE treatments in each of 7 adults, all of whom had functioning grafts 10 months later (52). Other series claim remission rates up to 80% in adults (64), and 88% in children (65). One large retrospective series concluded that modern immunosuppressive drug regimens do not reduce the recurrence rate of FSGS in adults, but that TPE achieved remission in 75% of cases (59). TPE has also been used prophylactically in cases at high risk of recurrence. However, in 34 pediatric transplant cases, prophylactic TPE posttransplant appeared not to confer any outcome benefit compared with treatment of actual recurrence (65).

TPE for FSGS in the native kidneys may be warranted if severe nephrotic problems persist despite full trials of corticosteroids and mycophenolate plus either cyclophosphamide or cyclosporine or rituximab. TPE (averaging 17 treatments), in combination with corticosteroids and cyclophosphamide, achieved sustained remissions in 8 of 11 previously unresponsive adults (66). In contrast, in another study, a shorter course of TPE (six treatments), without consistent immunosuppressive drugs, reduced proteinuria in only two of eight patients (67).

Plasmapheresis on protein A and anti-IgG columns has been reported as effective in small series of FSGS (68,69). How this could work is obscure, as the target molecules are not immunoglobulins. Their molecular size is smaller than albumin, so “double filtration” cannot be recommended either. LDL-apheresis, which can help control the hypercholesterolemia of severe nephrotic syndrome, has, in some FSGS cases, been claimed also to reduce proteinuria (70,71). However, conventional TPE with concurrent immunosuppression is the only well-proven treatment option for recurrent FSGS.

**Myeloma Cast Nephropathy**

Controversy continues regarding the place of TPE in the management of myeloma cast nephropathy. It occurs in patients with high circulating levels of free immunoglobulin light chains (FLC, either kappa or lambda). FLC are filtered at the glomerulus and enter the tubular fluid in amounts that overwhelm proximal
reabsorption and are toxic to tubule cells. With further concentration down the nephron, the excess light chains co-precipitate with Tamm–Horsfall protein to produce casts that block the lumens.

Logically, any intervention that can sufficiently lower the level of light chains in the blood can halt this process. However, renal recovery may not occur if the pathology is too far advanced (72). In addition, myeloma patients often have other causes of renal dysfunction that can contribute to poor responses to treatment. These include hypercalcemia, dehydration, plasma cell infiltration, renal amyloidosis, light chain glomerulopathy, pyelonephritis, and hyperuricemia. Therefore, the differing results of clinical trials of TPE may depend as much on whether or not these confounding factors were present as on the timeliness and thoroughness of TPE treatment. Also, other treatments clearly affect outcomes: rehydration and alkaline diuresis may help in the acute stages, and TPE will not succeed without concurrent treatment to reduce myeloma protein production (corticosteroids, melphalan, thalidomide, lenalidomide, bortezomib, etc.)

TPE has the best chance of saving kidney function when myeloma cast nephropathy presents acutely. The first RCT found major improvement in renal function in 13 of 15 patients who received 5 consecutive days of TPE, and in only 2 of 14 without TPE (73). The next RCT was small and found that the overall outcome with TPE was the same as in the control group; however, the TPE group contained more cases with severe renal failure, yet those who recovered from being dialysis-dependent (72). The large Canadian RCT (58 received TPE, 39 controls) failed to show significant benefit from 5 to 7 sessions of TPE in a 10-day period (74). However, few renal biopsies were performed to confirm cast nephropathy, and no free light chain measurements were made.

The recent Mayo Clinic RCT showed that in patients with biopsy-proven cast nephropathy, if TPE achieved 50% reduction of FLC, then it was effective in reversing renal failure and extending survival (75). A similar outcome has been reported using hemo dialysis with the new “high cut-off” membrane (Gambro HCO 1100, Gambro, Inc., Lakewood, CO), which is still experimental in the United States. It has a pore size larger than FLC molecules, but smaller than albumin, and can markedly reduce FLC levels (76). When treatment was early and without interruption, 13 patients recovered renal function (77).

On balance, we believe that TPE with simultaneous chemotherapy can be recommended in patients with recent-onset cast nephropathy, especially if biopsy-proven, and is often effective if applied early and intensively enough to rapidly reduce FLC levels. This may mean that TPE daily for 5 days and then every other day until FLC production has lessened. However, if this window of opportunity is lost, prolonged TPE is not justified.

**Glomerular Deposition Diseases**

Light chains can also deposit in glomeruli to cause renal pathology, as can immunoglobulin heavy chains. Light chain nodular glomerulopathy, which is more often due to kappa chain than lambda chain deposition, has been reported in a few cases to respond acutely to TPE (78,79). However, most studies of light chain and heavy chain glomerular deposition disease emphasize the poor renal prognosis and the need for intensive cytotoxic therapy, and do not address the role of TPE (80–83). Data are inadequate to make clear recommendations.

TPE has been unrewarding in the fibril-deposition glomerulopathies, of which renal amyloidosis is the most common. These are all recognized by the electron microscopy finding of “organized deposits” in the mesangium and capillary walls (84). All may recur in transplants, confirming the blood-borne origin of the glomerular deposits (85). Renal amyloidosis (8–12 nm diameter fibrils) does not respond to TPE, except in atypical cases, where it is complicated by crescentic nephritis (86). Fibrillary GN (randomly arrayed 15–30 nm diameter fibrils) is under-diagnosed, being recognizable in 0.5–1% of glomerular disease biopsies. It has been treated several times with immunosuppression and TPE, but results are not encouraging (87,88). Immuno tactoid GN (20–50 nm diameter microtubular deposits) is rare, with TPE treatment reported in three cases without success (89).

**Waldenstrom’s and Type I Cryoglobulin Renal Diseases**

Waldenstrom’s macroglobulinemia may cause hyperviscosity sufficient to produce mild renal impairment. Although severe renal damage is rare, cases of IgM thrombi occluding glomerular capillaries have been described (90,91). IgM depletion is effective and can usually be achieved by infrequent TPE procedures, because at least 80% of IgM is intravascular, and there is very little rebound of blood levels after a single TPE (92). Some monoclonal IgM proteins polymerize in the cold and are therefore properly called type I (monoclonal) cryoglobulins. Also, monoclonal IgG and IgA can be cryoglobulins or cause hyperviscosity syndrome, impairing kidney function and other organs. As with other IgG- or IgA-mediated diseases, several TPE procedures are required to clear these effectively (92).

**Hepatitis C and Type II & III Cryoglobulinemic Renal Diseases**

Whereas type I cryoglobulins are by definition monoclonal, Type II and Type III are referred to as “mixed cryoglobulins” because they contain both IgG and IgM (93). Type II cryoglobulins are immune complexes of IgG antibodies and specific antigens (most commonly hepatitis C), augmented by a monoclonal rheumatoid factor (RF). A RF is an IgM with anti-IgG activity, so it binds to the IgG in the immune complex, and makes it large enough to become precipitable in the cold. Type III cryoglobulins also contain IgG and IgM, but the RF is a polyclonal IgM; these are seen in inflammatory
disorders, autoimmune disease, or infections (hepatitis A, B, and C and cytomegalovirus) (94,95).

Circulating mixed cryoglobulins can be detected in 40–60% of patients with HCV, although overt cryoglobulinemic vasculitis develops in fewer than 5% of cases (96). The most frequently targeted organs are skin (purpura, ulcers, necrotizing vasculitis), joints, nerves and kidney, and symptoms can range from none to severe (94,96,97). Cryoglobulinemia, in addition to causing renal vasculitis, can lead to an immune-complex-mediated GN (predominantly MPGN type 1, although RPGN is also reported) that is often acute in onset, usually severe and progressive, and is typically linked to type II cryoglobulinemia and HCV infection (93). HCV is a lymphotropic as well as hepatotropic virus (98,99). Infected B-lymphocytes resist apoptosis, leading to persistent plasma cell clones that produce excess polyclonal IgG and also IgM RFs (100). This explains why mixed cryoglobulinemia is treatable with anti-B-cell immunosuppressives.

Immunosuppressive therapy, such as corticosteroids, cyclophosphamide, and rituximab, has been used to treat severe cryoglobulinemic vasculitis and GN. However, in the case of HCV-induced cryoglobulinemia, immunosuppression can increase viral load and thereby increase the antigenic stimulus of cryoglobulin production. Therefore, for the treatment of HCV-related cryoglobulinemic renal disease, interferon is recommended when possible with the goal of reducing HCV viral loads, whereas ribavirin use is often limited by degree of renal dysfunction (93). When the cryoglobulinemia is associated with severe end organ damage, such as skin ulcerations, GN, and neuropathy, TPE can be efficient in removing circulating cryoglobulins, and is often used alone or in combination with immunosuppressants for both short- and long-term management (93,101). The objective of TPE is to remove the plasma cryoglobulins and pathogen component, thereby altering the antigen-antibody ratio, to eliminate cytokines, and to increase immune-complex clearance (95).

There have been no randomized trials on the use of TPE in cryoglobulinemia, but case series and case reports suggest 70–80% improvement with use of TPE (101,102). It is best to perform the TPE in a warm room with warmed lines and replacement solutions to avoid precipitation of the cryoglobulin. The usual treatment protocol with TPE is 1–1.5 plasma volume exchange every 1–3 days, with 5% albumin or plasma as replacement fluid (1). Double cascade filtration, which separates plasma out of whole blood in the first filter, and removes high MW proteins in second filter (such as IgM) has been used to treat cryoglobulinemia (101).

Another modality is cryofiltration or cryoglobulinapheresis, where plasma is cooled in extracorporeal circuit to remove cryoglobulins, then remaining plasma is warmed and returned to the patient (103). There is a single randomized trial showing benefit of immunoadsorption apheresis in HCV cryoglobulinemia who had not responded to conventional therapy (104). Low-density lipoprotein apheresis designed to remove apolipoprotein B-containing lipoproteins has been used to reduce HCV viral loads; however, the effect on viral load reduction is not maintained significantly after therapy (105).

**Membranoproliferative GN Type 2**

MPGN type 2 (dense deposit disease) is a rare glomerular disease characterized on kidney biopsy by ribbon-like deposition of electron-dense material within the GBM (106). Deposition can also occur in Bruch’s membrane of the eye, which leads to formation of drusen that cause deterioration in visual acuity in ~10% of patients (107). MPGN type 2 accounts for <20% of cases of MPGN in children (usually aged 5–15 years), and only a fraction of adult cases.

Spontaneous remission is rare, and approximately 50% of patients will progress to ESRD within 10 years of diagnosis (107). Clinical presentation can include hematuria, nephrotic range proteinuria, and persistently low-sodium C3 and CH50 levels. More than 80% of patients with MPGN type 2 are positive for serum C3 nephritic factor (C3NeF), an autoantibody directed against the C3 convertase of the alternative pathway of the complement cascade. A smaller subset of patients with MPGN type 2 have mutations in the Factor H gene, leading to low Factor H levels or low functional activity (106).

The prognosis of MPGN type 2 is poor, clinical remissions are rare, and currently there is no universally effective treatment. Steroids have failed to be of any benefit. Other therapies that have been tried include cyclophosphamide, rituximab, eculizumab, calcineurin inhibitors, triptolide, heparin, sulodexide, as well as TPE (106,107). As this disease is rare, there are no RCTs. TPE has been attempted successfully in a few patients in conjunction with immunosuppressants to remove serum C3NeF (108,109). Plasma exchange with FFP infusion has been used in patients with MPGN type 2 to replenish deficient or mutant Factor H (110). MPGN type 2 recurs in virtually all kidney transplants, and there are a few case reports describing improvement in graft function with TPE (111,112). It has been recommended that treatment with rituximab, plasma exchange or infusion, eculizumab, or sulodexide be initiated in the presence of end organ damage and continued for 6–12 weeks, and continuation of treatment determined by improvement in hematuria or proteinuria, as well as reduction in C3NeF (106).

**TTP, Hemolytic Uremic Syndrome, and Pregnancy-Related Thrombocytopenic Renal Syndromes**

TTP and hemolytic uremic syndrome (HUS) in adults are clinically overlapping entities, characterized by a potentially life-threatening disseminated thrombotic microangiopathy. The classic pentad of symptoms that includes microangiopathic hemolytic anemia, thrombocytopenia, fever, neurologic deficits, and renal impairment only occurs in one-sixth of cases. Three entities have been defined based on main target organ: HUS exclusively affecting the kidneys, TTP/HUS
affecting kidneys and CNS, and HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) always involving liver and placenta in association with pre-eclampsia (113).

The incidence for idiopathic TTP is estimated to be 3.7 annually per million persons. It has been well established that use of plasma exchange in TTP reduces the mortality rate from 90% to ~20% (114). Although most cases are idiopathic, TTP can also occur in association with pregnancy, autoimmune diseases, infection, drugs such as cyclosporine A, FK, mitomycin, or ticlopidine, and bone marrow transplantation (115). For many patients with idiopathic TTP, the underlying defect is deficiency of the von Willebrand’s factor cleaving protease, ADAMTS13 caused by IgG inhibitors, a member of the a disintegrin and metalloprotease with thrombospondin type 1 motifs family of metalloproteases (115).

ADAMTS13 prevents accumulation of the “unusually large” VWF multimers. The pathophysiology of TMA-associated syndromes is hypothesized to be a direct insult to the microvasculature endothelial cells stimulating release of unusually large von Willebrand factor multimers from endothelial cells, which activate and promote adhesion and formation of occlusive platelet aggregates leading to ischemic organ damage. Moreover, the endothelial injury triggers contact activation of coagulation and formation of fibrin strands that adhere to the site of injury leading to the formation of the pathognomonic schistocytes seen on peripheral blood smear (113).

Plasma exchange serves to replenish the deficient ADAMTS13 metalloprotease and remove any circulating inhibitory antibodies (115). About 44–65% of patients with low ADAMTS13 activity will also have a detectable inhibitor present. Plasma ADAMTS13 activity can be normal to slightly decreased in patients with TTP related to bone marrow transplantation, cancer, drugs, or pregnancy, and these patients tend to have a higher mortality rate even with plasma exchange than those with idiopathic TTP (115). Determination of ADAMTS13 activity helps to differentiate atypical HUS from TTP.

HUS is a thrombotic microangiopathic pathology characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. In contrast to TTP, inhibition of von Willebrand’s factor-cleaving protease is rare with HUS, and there has been no clear-cut demonstration that removal of specific circulating factors by TPE alters the outcome. However, use of TPE in adults with HUS due to outbreaks of Escherichia coli O 157:H7 has been reported to be effective (116). In children with infection-induced HUS, supportive care is mainstay of therapy, corticosteroids, plasma infusion or exchange have no role, although some children with severe Streptococcus pneumoniae-induced HUS may benefit from TPE (113).

In atypical HUS (non-infection related), mutations in four regulatory proteins in the alternative pathway of complement activation have been identified to play a role in pathogenesis; complement factor H (CFH), membrane cofactor protein (MCP), complement factor I (CFI) and thrombomodulin (THBD), as well as two proteins of the C3 convertase (C3 and factor B) (117). Anti-CFH autoantibodies have also been identified. Treatment of atypical HUS can include plasma infusion (60-65ml of FFP/kg/week followed by 20ml/kg/week for maintenance) in order to replenish CFH, CFI, CFB and C3. TPE should be initiated urgently as it may be more effective than plasma infusion, and 25% of children will progress to ESRD after the first episode. TPE removes mutant CFH, CFI, CFB and C3, and anti-CFH autoantibodies, and FFP can be given to replenish normal amounts of these proteins while preventing complications such as volume overload. A typical TPE regimen is daily for 5 days, five times a week for 2 weeks, then three times a week for 2 weeks, and reassessment (1).

Plasma exchange is the most effective way to administer large quantities of FFP to replace depleted or inactivated factor, as well as removing the circulating ultralarge vWF multimers. TPE (with FFP replacement) should be started as soon as the diagnosis of severe TTP/HUS has been established. Presence of severe MAHA and otherwise unexplained thrombocytopenia are sufficient enough indicators for plasmapheresis (113). PAI has been reported to be more effective than TPE in refractory cases of TTP/HUS and cancer/chemotherapy-induced TTP/HUS (118). Circulating immune complexes have been implicated in a causative role, but the mechanism by which PAI might help is speculative.

TTP can occur in pregnancy, and should be treated with TPE (with FFP replacement), which is well-tolerated in pregnancy (119). However, caution should be exercised in interpreting ADAMTS13 levels, which are slightly low in normal pregnancy, lower in preeclampsia, and as low as 12–43% of normal in women with HELLP syndrome (120–122). Diagnostic tips include that liver enzyme elevations are very rare in TTP, and ADAMTS13 levels below 5% of normal are never seen in HELLP (123). HELLP syndrome causes renal impairment in 50% of cases, but TPE treatment is not necessary unless thrombocytopenia fails to improve by the fourth or fifth postpartum day, in which case, treatment with TPE (with FFP replacement) may be beneficial (124–126). Exacerbations of Upshaw–Schulman syndrome (congenital deficiency of ADAMTS13) can cause renal impairment and thrombocytopenia in pregnancy, and may mimic TTP (autoantibody-type) or HELLP; TPE is not needed, but without correct treatment (FFP infusion), fetal outcomes may be impaired (127).

Postpartum HUS in the past carried a mortality rate of 50%, and half of survivors progressed to end stage renal failure (128). Although often regarded as a separate entity from other forms of HUS, factor H polymorphisms may account for some cases (129). TPE (with FFP replacement) is recommended and may reduce mortality risk (128,130).

Catastrophic Antiphospholipid Syndrome

Antiphospholipid syndrome is an acquired hypercoaguable state due to autoantibodies directed at cardiolipins or β2-glycoprotein. CAPS is an extreme clinical presentation of this disease with thromboses.
occuring acutely in at least three organ systems, often damaging the kidneys, lungs, brain, skin, and other sites (131). TPE (with FFP replacement) removes the autoantibody and probably restores a more normal balance of antithrombotic plasma factors (1,132). Treatment recommendations include corticosteroids and anticoagulants as well as TPE or IVIG (133). Improved outcomes and survival have been analyzed, and TPE appears to be a critically important element in treatment (132–136). Most cases receive TPE daily for 3–5 days, or longer depending on clinical response. TPE is recommended also for CAPS during pregnancy (136).

Kidney Transplantation

ABO-incompatible kidney transplantation causes hyperacute rejection, due to preformed anti-A or anti-B antibodies in the recipient who lacks these antigens. Transplantation across ABO barriers from living donors became possible with the advent of pretransplant treatment of the recipient to deplete these alloantibodies. The number of such transplants increased until the last few years, when “paired donor” swapping has enabled more recipients to find better-matched living donors (137). Blood group antigen A2 is expressed less abundantly than A1 or B, making pretransplant antibody depletion more successful, and chronic antibody-mediated rejection (AMR) less likely, with A2 kidney transplants than other ABO mismatches (138).

Pretransplant regimens for ABO-mismatched kidneys no longer routinely include splenectomy (139,140). Most employ two to four TPE procedures together with IVIG (intravenous immunoglobulin) infusion, and sometimes rituximab. The goal is to reduce ABO antibody titers below 1:8, at which point, outcomes can approach those in cases with no ABO incompatibility (139–141). Published regimens include conventional TPE (albumin replacement), double-filtration plasmapheresis, and plasma immunoadsorption on ABO-antigen-specific columns (140,142,143). If FFP is given during TPE or for transfusion, it must be ABO-matched for the donor’s blood group, whereas RBC transfusion needs to be compatible with the recipient’s blood group. TPE is usually needed several times in the 2 weeks following transplantation to keep blood group antibody levels low, but usually thereafter, it becomes unnecessary.

Anti-HLA alloantibodies that are donor-specific (DSA) also are a contraindication to transplantation unless they can be depleted to the point that the crossmatch becomes negative. IVIG alone has been successful for this purpose in many patients (144). However, combinations of TPE, IVIG, and rituximab achieve desensitization in a greater percentage of potential recipients, and with less subsequent rejection (145,146). Recipients with a living donor can be prepared for a specified transplant date in this way and can receive TPE in the days prior to surgery. A typical regimen would be daily TPE for 4 days or until the crossmatch is negative, and then continued after transplantation perhaps every other day for a week (146). TPE is most commonly conventional (with albumin replacement), but immunoadsorption on protein A columns also appears effective (147).

Patients awaiting a deceased donor kidney may receive IVIG and rituximab to reduce their panel reactive antibody levels. TPE for deceased donor transplantation is not common because there is not much time in which to do it after a specific donor has been identified. However, conventional TPE or immunoadsorption can be performed once immediately prior to surgery and repeated thereafter (148).

AMR (or “humoral rejection”) may occur soon after transplantation or at any time thereafter. Before C4d (complement factor 4d) immunostaining of transplant biopsies became routine for the detection of AMR, many cases may have been missed, because cell-mediated rejection is much more common, and more easily recognizable on light microscopy. AMR is mediated by DSA, which can be removed from the plasma by TPE (149). IVIG appears somewhat less effective on its own, and is often given in addition to TPE by infusion at the end of each TPE procedure (150). Rituximab or bortezomib may be given to reduce antibody production, in addition to continuing routine antirejection medications (151,152).

TPE in conjunction with these medications has achieved excellent results in reversing acute AMR in numerous series as compared with historical and concurrent controls (153–158). Again, conventional TPE is the usual, although immunoadsorption is probably equivalent. In one small RCT, immunoadsorption plasmapheresis plus conventional drug management appeared superior to drug management alone (159). Whatever technique is used, DSA levels should be monitored to make sure that depletion is being achieved.

Photopheresis is an apheresis procedure that is now widely used as an effective addition to the treatment of cell-mediated rejection of heart and lung transplants, as well as graft-versus-host disease (160–162). The procedure uses 8-methoxy-psoralen and ultraviolet light to induce apoptosis in collected white blood cells, which, on return to the patient, cause the immune response to move toward a clonally specific immune tolerance (160). This is mediated by an increase in regulatory T cells, an effect which has been documented also in patients receiving photopheresis for renal allograft rejection (163). However, despite several renal transplant series reporting favorable clinical outcomes, definitive studies have not yet been performed, and it is not yet in routine use for kidney transplant rejection (164–166).

Recurrence of many types of GN occurs after transplantation, including anti-GBM disease, ANCA-related disease, FSGS, and MPGN (60). These may be treated with TPE, as discussed above.

Conclusion

Plasmapheresis (TPE) is an important therapy for several kidney diseases, based on strong evidence form clinical trials and series, and embodied in well-established guidelines. In addition, there are some rarer renal conditions where the nephrology specialist may
appropriately use TPE, despite limited clinical evidence, based on increasingly sophisticated insights into the molecular pathogenesis of the disease. Knowledge of disease mechanisms is invaluable also in selecting the appropriate TPE modality; for instance, some online plasma purification methods may not be applicable to the removal of small or nonimmunoglobulin molecules. Photopheresis and other apheresis modalities are as yet rarely indicated in nephrology practice.

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